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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,155	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,14-21,30 and 35-41* is/are pending in the application.

4a) Of the above claim(s) *39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,14-21,30,35-38,40 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/28/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed 6/18/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 12/18/06 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/18/07 has been entered.

Claims 1, 3, 14-21, 30 and 35-41 are pending in the instant application.

Applicants cannot file an RCE to obtain continued examination on the basis of claims that are independent and distinct from the claims previously claimed and examined as a matter of right (i.e., applicant cannot switch inventions). See 37 CFR 1.145. Any newly submitted claims that are directed to an invention that is independent and distinct from the invention previously claimed will be withdrawn from consideration and not entered. An RCE is not the filing of a new application (see MPEP 706.07(h)).

Newly submitted claim 39 is directed to an invention that is independent or

distinct from the invention originally claimed for the following reasons: The invention of claims 1, 3, 14-21, 30, 35-38, 40 and 41 (product claims) are related to the invention of newly added claim 39 (process claim) as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the method of inhibiting the expression of VEGFr1 and VEGFr2 can be practiced with another materially different product, for example a single stranded antisense oligonucleotide. Since the inventions are distinct, to search for more than one of the inventions in the same application would not necessarily return art against the other invention and therefore presents an undue search and corresponding examination.

Since applicant has received an action on the merits for the originally presented invention (the product), this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 39 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Applicant's amendments and/or arguments filed 6/18/07, with respect to the rejection(s) of claim(s) under 35 USC 112 have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the instant claim amendments.

Response to Sequence Compliance

Applicant asserts that the revised sequence listing complies fully with the sequence listing rules. However, this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). This application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because the CRF is flawed technically and could not be entered into the database. Therefore, SEQ ID NOs: 2752 and 2753, as instantly recited, could not be searched or examined. Therefore, the claims were searched and examined strictly based on the gene name rather than the specific sequence. Please see the attached Raw Sequence Listing Error Report for details.

A complete response to this office action must correct the defects cited above regarding compliance with the sequence rules and a response to the action on the merits which follows.

The aforementioned instance of failure to comply is not intended as an exhaustive list of all such potential failures to comply in the instant application. Applicants are encouraged to thoroughly review the application to ensure that the entire application is in full compliance with all sequence rules. This requirement will not be held in abeyance.

Response to Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The prior-filed applications do not teach molecules with each of the instant structural considerations wherein the antisense strand comprises 18-27 nucleotides that are complementary to a VEGFR1 RNA sequence comprising SEQ ID NO: 2752 or a portion thereof and VEGFR2 RNA sequence comprising SEQ ID NO: 2753 or a portion thereof and wherein the sense strand is complementary to the antisense strand and comprises an 19 to 27 nucleotide portion of VEGFR1 and VEGFR2 RNA. The instant claims further necessitate that about 50 to 100 percent of the nucleotides of each strand are chemically modified with specific modifications.

Applicant points to PCT/US03/05022 and 60/363,124 for support for each of the GenBank accession numbers representing instant SEQ ID NOs: 2752 and 2753. Although these documents disclose the GenBank accession number as possible target sequences, these documents do not teach molecules of the instant claims that are specific for both sequences simultaneously. Therefore, the instant claims are accorded an effective filing date of 1/12/04, which is that of the instant application.

Should applicants disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist in each of the priority documents.

Response to Double Patenting

Claims 1, 3, 14-21, 30, 35-38, 40 and 41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-30 of copending Application No. 10/664,668 and claims 49-51 and 58-76 of copending Application No. 10/444,853.

Applicant has requested consideration of filing a terminal disclaimer upon allowance of the pending claims.

New Objections/Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 14-21, 30, and 35-38, are rejected under 35 U.S.C. 102 (a) or (e) as being anticipated by Lockridge et al. (US 2003/0216335 A1).

The instant claims are directed to a chemically modified nucleic acid molecule comprising a sense and an antisense strand wherein each strand is 18 to 27 nucleotides in length, the antisense strand comprises 18 to 27 nucleotides that are complementary to a VEGFR1 RNA sequence comprising SEQ ID NO: 2752 or a portion thereof and VEGFR2 RNA comprising SEQ ID NO: 2753 or a portion thereof, the sense strand comprises an 18 to 27 portion of the VEGFR1 and VEGFR2 RNA and is complementary to the antisense strand, about 50 to 100 percent of the nucleotides in each strand are chemically modified with modifications selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications, and one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2'-O-methyl purines and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2'-deoxy-2'-fluoro pyrimidine nucleotides. The invention is further directed to types of modifications and a composition comprising the molecule in a pharmaceutically acceptable carrier or diluent. As explained in the sequence compliance section above,

SEQ ID NOs: 2752 and 2753 could not be searched or examined because applicant has not complied with the sequence rules. Therefore, the claims were searched and examined strictly based on the gene names rather than the recited sequences.

The disclosure of Lockridge et al. is applied as prior art because, although Lockridge et al. is claimed in the instant application for the benefit of a prior-filed application, the disclosure of Lockridge et al. is not considered to provide support a claim to the benefit of priority of an earlier filed document as above. However, although the disclosure of Lockridge et al. (as supported by Provisional Application 60/334,461) does not provide support for the instant claim limitation "about 50 to 100 percent of the nucleotides" in each strand are chemically modified with the instant modifications, Lockridge teaches an embodiment wherein the double stranded nucleic acid does not comprise any ribonucleotides and is therefore 100% modified with 2'-deoxy modifications. Therefore, the teachings of Lockridge et al. do not offer support for the entire range that is instantly recited but do teach an embodiment that falls within the range and therefore is anticipatory.

Lockridge et al. disclose compositions comprising double stranded nucleic acid (dsNA) molecules that are targeted to VEGFR1 and VEGFR2 that are dsRNAs or siRNAs that comprise single stranded components that are sense and antisense strands that are 23 nucleotides in length (see pages 3-4 and 12, for example). Lockridge et al. disclose the modification of the dsNAs of their invention with 5' end and/or 3' end terminal cap moieties including inverted deoxy abasic moieties and terminal phosphorothioate internucleoside linkage, 2'-O-methyl, 2'-fluoro and 2'-H,

dsNAs that comprise 5' terminal phosphate groups on the antisense strand and pharmaceutical compositions comprising the nucleic acids of their invention (pgs. 3-5 and 9, for example).

Lockridge et al. teach that preferably the nucleic acid molecules of the present invention are modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-flouro, 2'-O-methyl, or 2'-H (see page 16).

Lockridge et al. teach that the siRNA molecules need not be limited to those molecules containing only RNA, but further encompasses chemically modified nucleotides and non-nucleotides. In certain embodiments the invention features short interfering nucleic acids that do not require the presence of nucleotides having a 2'-hydroxy group for mediating RNAi and as such, short interfering nucleic acid molecules of the invention optionally do not contain any ribonucleotides. Optionally, the siRNA molecules can contain 5, 10, 20, 30, 40 or 50% ribonucleotides (see page 9). Therefore, Lockridge et al. teach dsNA molecules comprising ribonucleotides, dsNA molecules that are 100% 2'-deoxy modified and do not comprise ribonucleotides, as well as those comprising varying percentages of ribonucleotides.

Therefore, the instant invention is anticipated by Lockridge et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 14-21, 30, 35-38, 40 and 41 are rejected under 35 U.S.C. 103(a) as being obvious over Lockridge et al. (US 2003/0216335 A1), as applied in the rejection under 35 USC 102 (a) or (e) above, in view of Elbashir et al. (The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The instant claims are directed to a chemically modified nucleic acid molecule comprising a sense and an antisense strand wherein each strand is 18 to 27

nucleotides in length, the antisense strand comprises 18 to 27 nucleotides that are complementary to a VEGFR1 RNA sequence comprising SEQ ID NO: 2752 or a portion thereof and VEGFR2 RNA comprising SEQ ID NO: 2753 or a portion thereof, the sense strand comprises an 18 to 27 portion of the VEGFR1 and VEGFR2 RNA and is complementary to the antisense strand, about 50 to 100 percent of the nucleotides in each strand are chemically modified with modifications selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications, and one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2'-O-methyl purines and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2'-deoxy-2'-fluoro pyrimidine nucleotides. The invention is further directed to types of modifications, overhangs, and a composition comprising the molecule in a pharmaceutically acceptable carrier or diluent. As explained in the sequence compliance section above, SEQ ID NOs: 2752 and 2753 could not be searched or examined because applicant has not complied with the sequence rules. Therefore, the claims were searched and examined strictly based on the gene names rather than the recited sequences.

The disclosure of Lockridge et al. is applied as prior art because, although Lockridge et al. is claimed in the instant application for the benefit of a prior-filed application, the disclosure of Lockridge et al. is not considered to provide support a claim to the benefit of priority of an earlier filed document as above. However, although the disclosure of Lockridge et al. (as supported by Provisional Application 60/334,461)

does not provide support for the instant claim limitation "about 50 to 100 percent of the nucleotides" in each strand are chemically modified with the instant modifications, Lockridge teaches an embodiment wherein the double stranded nucleic acid does not comprise any ribonucleotides and is therefore 100% modified with 2'-deoxy modifications. Therefore, the teachings of Lockridge et al. do not offer support for the entire range that is instantly recited but do teach an embodiment that falls within the range and therefore is anticipatory.

Lockridge et al. disclose compositions comprising double stranded nucleic acid (dsNA) molecules that are targeted to VEGFR1 and VEGFR2 that are dsRNAs or siRNAs that comprise single stranded components that are sense and antisense strands that are 23 nucleotides in length (see pages 3-4 and 12, for example). Lockridge et al. disclose the modification of the dsNAs of their invention with 5' end and/or 3' end terminal cap moieties including inverted deoxy abasic moieties and terminal phosphorothioate internucleoside linkage, 2'-O-methyl, 2'-fluoro and 2'-H, dsNAs that comprise 5' terminal phosphate groups on the antisense strand and pharmaceutical compositions comprising the nucleic acids of their invention (pgs. 3-5 and 9, for example).

Lockridge et al. teach that preferably the nucleic acid molecules of the present invention are modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-flouro, 2'-O-methyl, or 2'-H (see page 16).

Lockridge et al. teach that the siRNA molecules need not be limited to those molecules containing only RNA, but further encompasses chemically modified nucleotides and non-nucleotides. In certain embodiments the invention features short interfering nucleic acids that do not require the presence of nucleotides having a 2'-hydroxy group for mediating RNAi and as such, short interfering nucleic acid molecules of the invention optionally do not contain any ribonucleotides. Optionally, the siRNA molecules can contain 5, 10, 20, 30, 40 or 50% ribonucleotides (see page 9). Therefore, Lockridge et al. teach dsNA molecules comprising ribonucleotides, dsNA molecules that are 100% 2'-deoxy modified and do not comprise ribonucleotides, as well as those comprising varying percentages of ribonucleotides.

Lockridge et al. do not teach modified 3'-overhangs of 1-3 nucleotides.

Elbashir et al. teach siRNAs, wherein each strand is 21-23 nucleotides in length and wherein at least 19 nucleotides of the sense strand are complementary to the antisense strand. Elbashir et al. teach chemical modification with 2'-deoxy or 2'-O-methyl modifications. Elbashir et al. teach that duplexes of 21 nt siRNAs with 2 nt 3' overhangs were the most efficient triggers of RNAi (see abstract). Elbashir et al. teach that chemical modifications were well tolerated in the overhang nucleotides and teach that the overhangs are deoxythymidines.

It would have been obvious to incorporate 2 nt 3' chemically modified overhangs, as taught by Elbashir et al. into the dsNA molecules of Lockridge et al.

One would have been motivated to incorporate 2 nt 3' chemically modified overhangs into the dsNA molecules of Lockridge et al. because Elbashir et al. teach that

duplexes of 21 nt siRNAs with 2 nt 3' overhangs were the most efficient triggers of RNAi and that chemical modifications, such as 2'-deoxy or 2'-O-methyl modifications, are well tolerated in the terminal nucleotides.

One would have a reasonable expectation of success given that Elbashir teaches that duplexes of 21 nt siRNAs with 2 nt 3' overhangs were the most efficient triggers of RNAi and that chemical modifications, such as 2'-deoxy or 2'-O-methyl modifications, are well tolerated in the terminal nucleotides and Lockridge et al. teach extensively modified dsNA molecules. One would reasonably expect for the modified overhangs of Elbashir et al. to benefit the siRNA molecules of Lockridge as well, as each are utilized for the same purpose of silencing target gene expression in a sequence specific manner via the RNAi mechanism.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 3, 14-21, 30, 35-38, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al. (The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888), in view of Sirois et al. (US 2003/0186920 A1), Hammond et al. (Nature, 2001, Vol. 2, pages 110-119), Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000), Matulic-Adamic et al. (US 5,998,203), Braasch et al. (Biochemistry,

2002, Vol. 41, No. 14, pages 4503-4510), and Olie et al. (Biochimica et Biophysica Acta, 2002, 1576, pages 101-109).

The instant claims are directed to a chemically modified nucleic acid molecule comprising a sense and an antisense strand wherein each strand is 18 to 27 nucleotides in length, the antisense strand comprises 18 to 27 nucleotides that are complementary to a VEGFR1 RNA sequence comprising SEQ ID NO: 2752 or a portion thereof and VEGFR2 RNA comprising SEQ ID NO: 2753 or a portion thereof, the sense strand comprises an 18 to 27 portion of the VEGFR1 and VEGFR2 RNA and is complementary to the antisense strand, about 50 to 100 percent of the nucleotides in each strand are chemically modified with modifications selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications, and one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2'-O-methyl purines and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2'-deoxy-2'-fluoro pyrimidine nucleotides. The invention is further directed to types of modifications, overhangs, and a composition comprising the molecule in a pharmaceutically acceptable carrier or diluent. As explained in the sequence compliance section above, SEQ ID NOs: 2752 and 2753 could not be searched or examined because applicant has not complied with the sequence rules. Therefore, the claims were searched and examined strictly based on the gene names rather than the recited sequences.

Elbashir et al. teach siRNAs, wherein each strand is 21-23 nucleotides in length

and wherein at least 19 nucleotides of the sense strand are complementary to the antisense strand. Elbashir et al. teach chemical modification with 2'-deoxy or 2'-O-methyl modifications with successful RNAi activity. Elbashir et al. teach that duplexes of 21 nt siRNAs with 2 nt 3' overhangs were the most efficient triggers of RNAi (see abstract). Elbashir et al. teach that chemical modifications were well tolerated in the overhang nucleotides and teach that the overhangs are deoxythymidines. Elbashir et al. teach that a 5'-phosphate on the antisense strand of a siRNA duplex is required for siRNA function (see page 6886). The instant specification does not define "terminal cap" and it is not a term of the art. Therefore, the terminally modified nucleotides of Elbashir et al. are considered to have a terminal cap.

Elbashir et al. do not teach siRNA molecules that are specific for VEGFR1 and VEGFR2. Elbashir et al. do not teach the combination of 2'-deoxy and 2'-O-methyl modifications in the same duplex, as recited in claim 1 part (f). Elbashir et al. does not teach 2'-deoxy-2'fluoro or phosphorothioate modifications, inverted deoxy abasic moieties or pharmaceutical carriers or diluents.

It is noted that the instant claims do not necessitate any specific resultant activity of the molecules. Elbashir et al. teach siRNA molecules wherein 100% of the nucleotides in the sense or antisense strand comprise 2'-deoxy or 2'-O-methyl modifications that did not retain activity. However, the "about 50 to 100 percent" modification required by the instant claims is not closed to 2'-deoxy or 2'-O-methyl modifications.

Sirois et al. teach antisense oligonucleotides that are homologous to and inhibit

the expression of both flt-1 (VEGFR1) and flk-1 (VEGFR2) genes (pg. 5, [0047]). Sirois et al. disclose that antisense oligonucleotides are commonly used as research and diagnostic reagents and that they are able to inhibit gene expression with exquisite specificity and are often used by those of skill in the art to elucidate the function of particular genes, to distinguish the functions of various members in a biochemical pathway or are harnessed for therapeutic use (pg. 1, [0008]). Sirois et al. teach that such oligonucleotides can be used to reduce VEGF-induced inflammation and angiogenesis, for example, pathological angiogenesis, in mammals. Sirois et al. disclose that chemical modification of the antisense oligonucleotides of the invention can improve stability and intracellular incorporation (pg. 6, [0059]) and provide an extensive teaching of internucleoside linkage, nucleobase and sugar modifications that can be made to antisense oligonucleotides including phosphorothioate linkages, 2'-F, 2'-O-me and 2'-H (deoxy) wherein the modifications can be 3' terminal or 5' terminal modifications (pgs. 7-8). Sirois et al. teach compositions comprising the oligonucleotides and pharmaceutically acceptable carriers or diluents.

Hammond et al. teach two methods for silencing specific genes, antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from questionable specificity and incomplete efficacy (see page 110, column 1). Hammond et al. teach that dsRNAs have been shown to inhibit gene expression in a sequence-specific manner and that RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression.

Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures. The enzymatic RNA molecules of Matulic-Adamic et al. are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3' phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example). For example, figure 3 contains a ribozyme structure that encompasses modification of at least 20%, at least 30%, at least 40% or at least 50% of the nucleotide positions, as well as the modifications instantly claimed. The modifications can be in one or both of the strands and can be modifications of different types within the same structure.

Parrish et al. teach a chemically synthesized siRNA molecule, wherein each strand is 26 bp in length. Additionally, Parrish et al. teach a 742 nt long dsRNA with complete modification with 2'-fluorouracil modifications.

Braasch et al. teach that the need for antisense oligomers that are more potent and more selective has been widely recognized and has led to the development of

chemical modifications to improve binding and selectivity (see page 4503). Braasch et al. teach goals for improving oligonucleotides including: improve pharmacokinetics, tissue distribution, and targeting; characterize the mechanism of RNA interference and its full potential for inhibition of gene expression for cell culture studies; use RNAi for in vivo inhibition of mammalian gene expression; perform comparative studies to demonstrate the relative strengths of different oligomer chemistries for given applications (i.e. morpholino versus RNAi) (see Table 2). Braasch et al. teach that if good *in vivo* uptake can be achieved, RNAi might significantly improve the ability of oligonucleotides to have an impact (see page 4509).

Olie et al. teach that gapmer oligonucleotide chemistry, wherein three distinct regions are present, has provided antisense oligonucleotides with increased efficacy and reduced non-antisense-related toxicity. Olie et al. added chemical modifications to ribonucleotides at either of the two ends of an oligonucleotide sequence, or the center region together with different combinations of phosphodiester/phosphorothioate backbones and investigated the effect on the activity of antisense oligonucleotides. The gapmer oligonucleotide exhibited a potent bispecific antisense activity. Olie et al. teach that gapmer chemistry is an optimal format and that these findings may have implications for the design and development of antisense oligonucleotides. Olie et al. teach that 2'-O-modifications provide additional nuclease resistance to oligonucleotides. Olie et al. teach synthesis of 20-mer chimeric antisense oligonucleotides.

It would have been obvious to synthesize a siRNA as taught by Elbashir et al. that is specific for VEGFR1 and VEGFR2, comparative to the antisense

oligonucleotides of Sirois et al. It would have been obvious to incorporate 2'-deoxy-2'fluoro modifications, as taught by Parrish et al., Sirois et al. and Matulic-Adamic et al. or phosphorothioate modifications, as taught by Sirois et al. and Matulic-Adamic et al. and to further to incorporate inverted deoxyabasic moieties or combine extensive modifications, as taught by Matulic-Adamic et al. It would have been obvious to incorporate a pharmaceutically acceptable carrier or diluent as taught by Sirois et al.

One would have been motivated to synthesize a siRNA as taught by Elbashir et al. that is specific for VEGFR1 and VEGFR2, because Sirois et al. teach antisense oligonucleotides that are directed to VEGFR1 and VEGFR2 and teach that such oligonucleotides can be used to reduce VEGF-induced inflammation and angiogenesis, for example, pathological angiogenesis, in mammals. Since Hammond et al. teach that utilizing a dsRNA is a preferable method to using antisense oligonucleotides because dsRNAs have been shown to inhibit gene expression in a sequence-specific manner and RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression, one would have been motivated to utilize a dsRNA instead of an antisense oligonucleotide to target and inhibit VEGFR1 and VEGFR2 in a sequence specific manner.

One would have been motivated to incorporate 2'-deoxy-2'-fluoro modifications, as taught by Parrish et al., Sirois et al. or Matulic-Adamic et al., as well as phosphorothioate modifications, as taught by Sirois et al. and Matulic-Adamic et al., as well as to incorporate inverted deoxyabasic moieties or combine extensive modifications, as taught by Matulic-Adamic et al. because each of these chemical

modifications, as well as various combinations of chemical modifications, were known in the art to protect nucleic acids from exonuclease degradation and enhance the activity of nucleic acids, as taught by Matulic-Adamic et al. and Sirois et al.

The instant genus of chemical modifications were known in the antisense and ribozyme art. Furthermore, several of these modifications were incorporated into dsRNA molecules, as evidenced by Parrish et al. and Elbashir et al. It is considered that there would be some configuration of the chemical modifications that were known in the art to benefit other nucleic acid molecules such as antisense oligonucleotides or ribozymes that would retain RNAi activity when incorporated into nucleic acid molecules. The teachings of Elbashir et al. are considered to be motivation with regards to extensively modifying nucleic acid duplexes to optimize the activity therein. Although Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity, there are no instant claims that are identical in scope to the teachings of Elbashir et al. Therefore, within the genus of molecules that are being instantly claimed, the teachings of Elbashir et al. are considered to offer motivation to test various types of known chemical modifications at different percentages in order to optimize the activity of the molecule.

It is noted that ribozymes are sequence specific inhibitory nucleic acid molecules that rely on activity with a complex secondary structure. Although ribozymes are faced with the complexity of structure, it is well known in the nucleic acid art to incorporate extensive levels of chemical modification to enhance the activity of the molecule and to

specifically incorporate each of the instantly recited modifications, as evidenced by Matulic-Adamic et al.

The instant specification discloses a multitude of oligonucleotide and ribozyme art regarding chemical modifications and teaches that "Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis, and are incorporated by reference herein. In view of these teachings, similar modifications can be used as described herein to modify the siNA nucleic acid molecules of the instant invention so long as the ability of siNA to promote RNAi in cells is not significantly inhibited." (see pages 101 and 102).

It is acknowledged that the specification is not to be relied upon for a source of motivation and that is not considered to be the instant case. The specification is merely being relied upon to distinguish that applicant recognized that double stranded nucleic acid modification is dependent upon the state of the art of oligonucleotides and ribozymes and that previously beneficial chemical modifications would be used with double stranded nucleic acid molecules as well.

Therefore, one would have been motivated to incorporate chemical modifications at 1about 50 to 100% of the nucleotide positions of each strand because Elbashir et al. teach testing two types of chemical modifications extensively in siRNA molecules, and Parrish et al. and Matulic-Adamic et al. teach extensive chemical modification of nucleic acids with successful inhibition of target gene expression.

Furthermore, Braasch et al. teach that the need for antisense oligomers that are

more potent and more selective has been widely recognized and has led to the development of chemical modifications to improve binding and selectivity. Braasch et al. further recognize that goals to improve RNAi can be accomplished by utilizing chemical modifications. Since Braasch et al. teach that chemical modifications yield more potent and more selective antisense oligomers, such as oligomers for RNAi, and Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach modified double stranded nucleic acid molecules that inhibit target gene expression, the gene expression of Elbashir et al. and Parrish et al. being inhibited by RNAi, one would have been motivated to synthesize duplexes with different levels of modifications to optimize the activity of the molecule.

Additionally, antisense oligonucleotides, ribozymes, and dsRNAs are each commonly used for sequence-specific mRNA knockdown and each of these encounters the same problems for effective application. Therefore, one would have been motivated to utilize the same modifications and techniques that have been utilized to overcome these problems with antisense oligonucleotides or ribozymes with siRNAs to add the same benefits to RNAi technology.

For example, Olie et al. teach that gapmer oligonucleotide chemistry, wherein three distinct regions are present, has provided antisense oligonucleotides with increased efficacy and reduced non-antisense-related toxicity. Olie et al. teach that combinations of different modifications at different regions of the oligonucleotide have been tested in order to optimize oligonucleotide activity. Olie et al. teach stepwise experimentation of modifications throughout oligonucleotides in order to find the optimal

configuration. Olie et al. is relied upon as evidence that it is common to experiment with different known modifications at different locations to optimize oligonucleotide activity.

Therefore, one would have been motivated to apply such a method to incorporate known modifications at various locations and amounts, as taught by Olie et al., into the siRNA duplexes that were synthesized by Elbashir et al. (EMBO).

Finally, one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to antisense oligonucleotides, ribozymes or siRNA duplexes, as evidenced by Elbashir et al., Sirois et al., Matulic-Adamic et al., Parrish et al. and Olie et al., wherein each of the molecules face the same challenges, and each of which can be improved with modifications, as evidenced by Braasch et al. Since Olie et al. teach effectively walking modifications across antisense oligonucleotides to optimize the combination of modifications as well as the location of the modifications and Elbashir et al. and Parrish et al. teach successfully synthesizing modified double stranded nucleic acid molecules, one would reasonably expect for modifications at various percentages to benefit the double stranded nucleic acid molecules of Elbashir et al. targeted to VEGFR1 and VEGFR2, as evidenced by the antisense oligonucleotides targeting VEGFR1 and VEGFR2 of Sirois et al.

Since Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach extensive modification of double stranded nucleic acid molecules and Olie et al. teach experimentally determining optimal locations and levels of modification of antisense oligonucleotides, incorporating the modifications at various percentages in the double

stranded nucleic acid molecules of Elbashir et al. is considered within the realm of routine optimization.

It is noted that Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity. However, regardless of the results of these specific modifications at 100% of the positions of one or both strands, Elbashir et al. did modify duplexes and published data regarding successful inhibition with some duplexes and unsuccessful inhibition with others, supporting that testing of such known chemical modifications is routine in the art. The results of Elbashir et al. are considered to offer motivation to incorporate chemical modifications at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage.

Importantly, the instant claims recite "about" 50 to 100 percent of the nucleotides of each strand are chemically modified. Since Elbashir et al. teach successful inhibition with siRNA duplexes modified at 8/42 of the positions (19%) with 2'-deoxy modifications, this meets the instant limitation of "about" 50%.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

In addition to the pending double patenting rejections addressed above, the following serial numbers of co-pending applications contain claims in which an obviousness-type double patenting rejection would be applied:

11/369,108
10/944,611
10/962,898

It is Applicants' burden to file appropriate terminal disclaimers for all relevant applications listed above. Furthermore, if Applicants are aware of any pending applications or patents, which are not listed above, it is Applicants' duty to disclose these applications or patents, and to submit an appropriate terminal disclaimer over these applications or patents as pertinent to the instant invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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